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INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

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(21) International Application Number: PCT/US97/10024 (22) International Filing Date: 11 June 1997 (11.06.97) (30) Priority Data: 60/020,482 14 June 1996 (14.06.96) US (71) Applicant: KRITON MEDICAL, INC. [US/US]; George H. Gerstman, Two North LaSalle Street, Chicago, IL 60602 (US). (72) Inventor: FINE, Robert, B.; Apartment 1B, 36 West 69th Street, New York, NY 10023 (US). (74) Agent: GERSTMAN, George, H.; Gerstman, Ellis & McMillin, Ltd., Suite 2010, Two North LaSalle Street, Chicago, IL 60602 (US).		(81) Designated States: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, TJ, TM, TR, TT, UA, UG, UZ, VN, ARIPO patent (GH, KE, LS, MW, SD, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG). Published <i>With international search report.</i>
(54) Title: METHODS AND DEVICES FOR REDUCING ANGINA, ENHANCING MYOCARDIAL PERFUSION AND INCREASING CARDIAC FUNCTION (57) Abstract A method and apparatus for the treatment of disorders related to decreased myocardial perfusion and cardiac function is provided. A selected beam of radiation is directed to the patient's heart for a predetermined time period, and an angiogenic substance, capable of stimulating growth of blood vessels in the patient, is administered to the patient.		

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5 **METHODS AND DEVICES FOR REDUCING ANGINA,
 ENHANCING MYOCARDIAL PERFUSION AND
 INCREASING CARDIAC FUNCTION**

10

 This application claims the benefit of U.S. Provisional application
 Ser. No. 60/020,482 filed June 14, 1996.

15

BACKGROUND OF THE INVENTION

 The field of this invention concerns methods and devices for the
treatment of disorders related to decreased myocardial perfusion and cardiac
function, and, in particular, methods and devices for reducing angina pain,
enhancing myocardial perfusion and/or increasing cardiac function.

20

 Various surgical and pharmaceutical procedures have been used to
attempt to enhance myocardial perfusion and/or cardiac function. One such
procedure currently being evaluated in human clinical trials is transmyocardial
laser revascularization (TMLR) in which a laser is directed to the heart and
traverses the myocardium. Following TMLR, some patients have experienced a
25 dramatic reduction in angina pain. In addition, in some instances, TMLR has
resulted in significant improvements in myocardial perfusion and/or cardiac

function. In many cases, enhanced perfusion of the heart and/or cardiac function have persisted for at least six months.

TMLR as currently practiced has not shown success in all instances, however. Levels of success rates are also variable. In addition, some
5 patients, such as, for example, patients with an unprotected anterior myocardium or patients experiencing frank congestive heart failure, are presently not good candidates for receiving TMLR procedures.

In addition, the mechanism of TMLR is not clearly understood. One hypothesis, among others, is that channels in the heart resulting from TMLR
10 provide oxygenated blood to the diseased myocardium. Another hypothesis is that new vessels form in the myocardium surrounding laser channels resulting from TMLR. With respect to the aforementioned hypotheses, investigators have not yet convincingly proved channel persistence or meaningful new vessel formation and persistence in all cases of TMLR. Accordingly, procedures for forming
15 channels in the myocardium, such as forming channels with different types of lasers or mechanical elements, and forming channels in different lengths and directions, have also been discussed as alternative procedures for reducing angina pain, enhancing myocardial perfusion or increasing cardiac function.

Therefore, there exists a need to improve TMLR procedures,
20 and/or procedures involving the formation of channels in the myocardium of the heart, to better reduce angina pain, to enhance myocardial perfusion, to increase

cardiac function, and/or to expand the pool of patients who could benefit from such procedures.

SUMMARY OF THE INVENTION

5 Methods and devices are disclosed for reducing angina pain, enhancing myocardial perfusion and/or increasing cardiac function. The present invention is based on the novel recognition by the inventor that the administration to a patient of angiogenic substances capable of stimulating the growth of blood vessels in combination with TMLR procedures and/or procedures for forming
10 channels in the myocardium, can improve the reduction of angina pain, the enhancement of myocardial perfusion and/or the increase in cardiac function currently associated with TMLR procedures. In addition, the inventor has recognized that administering angiogenic substances in conjunction with TMLR procedures and/or procedures for forming channels in the myocardium can expand
15 the pool of patients who would benefit from treatment to reduce angina, to enhance myocardial perfusion and/or to increase cardiac function.

Myocardial perfusion, for the purposes of this invention, includes blood flow to the heart tissue including myocardium, sub-endocardium, endocardium, sub-epicardium, and/or epicardium.

20 Angiogenic substances, for the purposes of this invention, include substances capable of stimulating the growth of blood vessels.

Channels, for the purposes of this invention, include holes, lumens or passageways, and other perforations in the heart.

TMLR procedures, for the purposes of this invention, include procedures for directing a beam of radiation to heart tissue.

5

DETAILED DESCRIPTION OF THE INVENTION

In aspects of the invention, methods for reducing angina pain, enhancing myocardial perfusion and/or increasing cardiac function include directing a beam of radiation for a predetermined time period to the heart of a patient, and administering to the patient at least one angiogenic substance capable of stimulating the growth of blood vessels in the patient. In alternative embodiments of the invention, the method can involve producing the radiation from a laser, such as a carbon dioxide laser or other radiation producing elements known to those of ordinary skill in the art; and/or forming at least one channel in the myocardium. The channel forming step can include forming the channel to link epicardial and endocardial surfaces of the heart. The method can also be employed in conjunction with implanting and or removing at least one ventricular assist device (VAD). VADs hereinafter can include left, right or bi-ventricular assist devices.

20 In other embodiments of the invention, the angiogenic substance capable of stimulating the growth of blood vessels in the patient can include an angiogenic growth factor. The angiogenic growth factor can include vascular

endothelial growth factor (VEGF) vascular permeability factor (VPF) in native and/or non-native forms. The angiogenic growth factor also can include a fibroblast growth factor, such as a basic fibroblast growth factor (bFGF or FGF-2), in native and/or non-native forms, and/or acidic fibroblast growth factor
5 (aFGF or FGF-1), in native and/or non-native forms. Other examples of angiogenic substances include, but are not limited to, platelet-derived growth factor (PDGF) such as PDGF-AA, PDGF-BB, and PDGF-AB; hepatocyte growth factor/scatter factor (HGF/SF); placenta growth factor; endothelial cell growth factor (ECGF); platelet-derived endothelial cell growth factor (PD-ECGF); and
10 urokinase plasminogen activator (uPA). Other angiogenic substances for the growth of vessels known to those of ordinary skill in the art may be useful in the practice of this invention.

The angiogenic substance can be administered to the patient in a variety of ways. Examples of methods of administering the angiogenic substance
15 include one or more of the following steps; directly injecting the angiogenic substance into the atria, the ventricles, the veins, the arteries, and/or the formed channels; applying a slow-release formulation of the angiogenic substance into the formed channels; administering a slow-release formulation of the angiogenic substance orally, and/or via a skin patch; applying a material, such as a
20 biologically compatible or incompatible, resorbable or non-resorbable material, contacted with the angiogenic substance, over the surface of the heart; and

infusing the angiogenic substance into the patient via a pump connected to the atria, the ventricles, the veins, the arteries, and/or the formed channels.

Other examples of methods of administering the angiogenic substance include one or more of the following steps: implanting a catheter, such as a slow-release catheter, contacted with the angiogenic substance, into the atria, the ventricles, and/or the formed channels; loading a sleeve, such as an infusion sleeve, contacted with the angiogenic substance, over a catheter and introducing the catheter into the formed channels; applying bead carriers, such as heparin-alginate beads, contacted with the angiogenic substance, over the epicardial and/or endocardial surfaces of the heart; inserting an implant, such as a fibrin-glue implant, contacted with the angiogenic substance, between, for example, the aorta and the myocardium, and/or in other positions of the epicardial and/or endocardial surfaces; injecting retroviral and/or non-retroviral vectors enclosing a gene for the angiogenic substance into the myocardium, arterial walls and/or other areas of uptake, such as the skin, of the patient; infusing the angiogenic substance into veins and/or arteries; and inserting a stent, contacted with the angiogenic substance, into the formed channels. The stent can be biologically compatible or incompatible, resorbable or non-resorbable. Other methods of administration known to those of ordinary skill in the art may be useful in the practice of this invention.

In other aspects of the invention, methods for reducing angina pain, and/or enhancing myocardial perfusion and/or cardiac function include forming

at least one channel in the myocardium of a patient, and administering to the patient at least one angiogenic substance capable of stimulating growth of blood vessels in the patient. In alternative embodiments of the invention, the channel forming step can include forming the channel to link epicardial and endocardial surfaces of the heart. The method can also be employed in conjunction with implanting and/or removing a VAD. In other embodiments of the invention, the angiogenic substances and/or methods for administering the same discussed above can be used.

In still other aspects of the invention, methods for reducing angina pain, and/or enhancing myocardial perfusion and/or cardiac function include forming at least one channel in the myocardium of the patient, and inserting into the channel at least one stent contacted with one or a mixture of angiogenic substances capable of stimulating the growth of blood vessels in the patient. In embodiments of the invention, the stent can be biologically compatible or incompatible, and the channel forming step can include forming the channel to link epicardial and endocardial surfaces of the heart. The method can also include implanting and/or removing a VAD. The angiogenic substances and/or methods for administering the same discussed above can be used with these aspects of the invention.

In further aspects of the invention, devices for reducing angina pain, and/or enhancing the myocardial perfusion and/or cardiac function of a patient are disclosed that include a stent contacted with at least one angiogenic

substance capable of stimulating the growth of blood vessels in the patient and adapted for insertion into a channel formed in a myocardium of the heart of the patient. In embodiments of the invention, the stent can be biologically compatible or non-compatible, resorbable or non-resorbable. The devices of the invention
5 can be self-expanding; and/or can further include an element for expanding the stent from a first to a second position. The angiogenic substances discussed above can be used in these aspects of the invention.

In other aspects of the invention, devices for reducing angina in a patient and/or enhancing the myocardial perfusion and/or cardiac function of a
10 patient are disclosed that include an element for directing a selected beam of radiation for a pre-determined time period to a heart of the patient, and an element for administering to the patient at least one angiogenic substance capable of stimulating growth of blood vessels in the patient. The angiogenic substances discussed above can be used in these aspects of the invention.

15 In still other aspects of the invention, devices for reducing angina in a patient and/or enhancing the myocardial perfusion and/or cardiac function of a patient are disclosed that include an element for forming at least one channel in a myocardium in a heart of the patient, and an element for administering to the patient at least one angiogenic substance capable of stimulating growth of blood
20 vessels in the patient. The angiogenic substances discussed above can be used in these aspects of the invention.

In sum, the present invention benefits from the recognition that TMLR procedures and/or procedures for forming channels in the myocardium can be performed in conjunction with the administration of angiogenic substances capable of stimulating the growth of blood vessels in a patient. The methods and
5 devices of the present invention have several advantages over the prior art. In comparison with current TMLR procedures and/or procedures for forming channels in the myocardium, the present invention can improve in patients the level of angina pain reduction, and/or enhance myocardial perfusion and/or cardiac function. Accordingly, the present invention can improve the treatment
10 of disorders associated with reduced myocardial perfusion such as angina and/or improve cardiac functions in patients experiencing different levels of heart failure. In addition, the present invention can expand the pool of patients who can be eligible for TMLR procedures and/or procedures involving the formation of channels in the myocardium.

15 It will be understood that the above description pertains to only several embodiments of the present invention. That is, the description is provided by way of illustration and not by way of limitation. The invention is further characterized according to the following claims.

What Is Claimed Is:

1. A method for reducing angina in a patient comprising:

5 directing a selected beam of radiation for a predetermined time period to a heart of the patient; and

administering to the patient at least one angiogenic substance capable of stimulating growth of blood vessels in the patient.

10 2. A method for enhancing myocardial perfusion in a patient comprising:

directing a selected beam of radiation for a predetermined time period to a heart of the patient; and

15 administering to the patient at least one angiogenic substance capable of stimulating growth of blood vessels in the patient.

3. A method for enhancing cardiac function in a patient comprising:

directing a selected beam of radiation for a predetermined time period to a heart of the patient; and

20 administering to the patient at least one angiogenic substance capable of stimulating growth of blood vessels in the patient.

4. A method for reducing angina in a patient comprising:

forming at least one channel in a myocardium of the patient; and

administering to the patient at least one angiogenic substance

5 capable of stimulating growth of blood vessels in the patient.

5. A method for reducing angina in a patient comprising:

forming at least one channel in a myocardium of the patient; and

10 inserting at least one stent contacted with at least one angiogenic substance capable of stimulating growth of blood vessels in the patient into the channel.

6. An apparatus for reducing angina in a patient comprising:

15 a stent contacted with at least one angiogenic substance capable of stimulating growth of blood vessels in the patient and adapted for insertion into a channel formed in the myocardium of the patient.

7. An apparatus for reducing angina in a patient comprising:

means for directing a selected beam of radiation for a pre-determined time period to a heart of the patient; and

5 means for administering to the patient at least one angiogenic substance capable of stimulating growth of blood vessels in the patient.

8. An apparatus for reducing angina in a patient comprising:

10 means for forming at least one channel in a myocardium of the patient; and

means for administering to the patient at least one angiogenic substance capable of stimulating growth of blood vessels in the patient.

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US97/10024

A. CLASSIFICATION OF SUBJECT MATTER

IPC(6) :A61B 19/00

US CL :128/898; 623/1

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 128/898; 427/2.3, 2.25; 600/36; 604/890.1; 606/108; 623/1, 2, 12, 66, 900, 901

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

APS, DIALOG

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US 5,464,650 A (BERG et al.) 07 November 1995, entire document.	1-8
Y,P	US 5,527,337 A (STACK et al.) 18 June 1996, entire document.	1-8
Y	US 5,287,861 A (WILK) 22 February 1994, entire document.	1-8
A	US 5,429,144 A (WILK) 04 July 1995, entire document.	1-8
Y	LEE et al. Effects of laser irradiation delivered by flexible fiberoptic system on the left ventricular internal myocardium. American Heart Journal, September 1983. Volume 106 Number 3, pages 587-590.	1-8



Further documents are listed in the continuation of Box C.



See patent family annex.

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Date of the actual completion of the international search

18 AUGUST 1997

Date of mailing of the international search report

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INTERNATIONAL SEARCH REPORTInternational application No.
PCT/US97/10024**C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT**

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	ISNER et al. The Current Status of Lasers in Treatment of Cardiovascular Disease. IEEE Journal of Quantum Electronics. December 1984. Vol. QE-20. No. 12, pages 1406-1420.	1-8

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enhancing myocardial perfusion and/or increasing cardiac function.

20

 Various surgical and pharmaceutical procedures have been used to
attempt to enhance myocardial perfusion and/or cardiac function. One such
procedure currently being evaluated in human clinical trials is transmyocardial
laser revascularization (TMLR) in which a laser is directed to the heart and
traverses the myocardium. Following TMLR, some patients have experienced a
25 dramatic reduction in angina pain. In addition, in some instances, TMLR has
resulted in significant improvements in myocardial perfusion and/or cardiac

function. In many cases, enhanced perfusion of the heart and/or cardiac function have persisted for at least six months.

TMLR as currently practiced has not shown success in all instances, however. Levels of success rates are also variable. In addition, some
5 patients, such as, for example, patients with an unprotected anterior myocardium or patients experiencing frank congestive heart failure, are presently not good candidates for receiving TMLR procedures.

In addition, the mechanism of TMLR is not clearly understood. One hypothesis, among others, is that channels in the heart resulting from TMLR
10 provide oxygenated blood to the diseased myocardium. Another hypothesis is that new vessels form in the myocardium surrounding lased channels resulting from TMLR. With respect to the aforementioned hypotheses, investigators have not yet convincingly proved channel persistence or meaningful new vessel formation and persistence in all cases of TMLR. Accordingly, procedures for forming
15 channels in the myocardium, such as forming channels with different types of lasers or mechanical elements, and forming channels in different lengths and directions, have also been discussed as alternative procedures for reducing angina pain, enhancing myocardial perfusion or increasing cardiac function.

Therefore, there exists a need to improve TMLR procedures,
20 and/or procedures involving the formation of channels in the myocardium of the heart, to better reduce angina pain, to enhance myocardial perfusion, to increase

cardiac function, and/or to expand the pool of patients who could benefit from such procedures.

SUMMARY OF THE INVENTION

5 Methods and devices are disclosed for reducing angina pain, enhancing myocardial perfusion and/or increasing cardiac function. The present invention is based on the novel recognition by the inventor that the administration to a patient of angiogenic substances capable of stimulating the growth of blood vessels in combination with TMLR procedures and/or procedures for forming
10 channels in the myocardium, can improve the reduction of angina pain, the enhancement of myocardial perfusion and/or the increase in cardiac function currently associated with TMLR procedures. In addition, the inventor has recognized that administering angiogenic substances in conjunction with TMLR procedures and/or procedures for forming channels in the myocardium can expand
15 the pool of patients who would benefit from treatment to reduce angina, to enhance myocardial perfusion and/or to increase cardiac function.

Myocardial perfusion, for the purposes of this invention, includes blood flow to the heart tissue including myocardium, sub-endocardium, endocardium, sub-epicardium, and/or epicardium.

20 Angiogenic substances, for the purposes of this invention, include substances capable of stimulating the growth of blood vessels.

Channels, for the purposes of this invention, include holes, lumens or passageways, and other perforations in the heart.

TMLR procedures, for the purposes of this invention, include procedures for directing a beam of radiation to heart tissue.

5

DETAILED DESCRIPTION OF THE INVENTION

In aspects of the invention, methods for reducing angina pain, enhancing myocardial perfusion and/or increasing cardiac function include directing a beam of radiation for a predetermined time period to the heart of a patient, and administering to the patient at least one angiogenic substance capable of stimulating the growth of blood vessels in the patient. In alternative embodiments of the invention, the method can involve producing the radiation from a laser, such as a carbon dioxide laser or other radiation producing elements known to those of ordinary skill in the art; and/or forming at least one channel in the myocardium. The channel forming step can include forming the channel to link epicardial and endocardial surfaces of the heart. The method can also be employed in conjunction with implanting and or removing at least one ventricular assist device (VAD). VADs hereinafter can include left, right or bi-ventricular assist devices.

20 In other embodiments of the invention, the angiogenic substance capable of stimulating the growth of blood vessels in the patient can include an angiogenic growth factor. The angiogenic growth factor can include vascular

endothelial growth factor (VEGF) vascular permeability factor (VPF) in native and/or non-native forms. The angiogenic growth factor also can include a fibroblast growth factor, such as a basic fibroblast growth factor (bFGF or FGF-2), in native and/or non-native forms, and/or acidic fibroblast growth factor 5 (aFGF or FGF-1), in native and/or non-native forms. Other examples of angiogenic substances include, but are not limited to, platelet-derived growth factor (PDGF) such as PDGF-AA, PDGF-BB, and PDGF-AB; hepatocyte growth factor/scatter factor (HGF/SF); placenta growth factor; endothelial cell growth factor (ECGF); platelet-derived endothelial cell growth factor (PD-ECGF); and 10 urokinase plasminogen activator (uPA). Other angiogenic substances for the growth of vessels known to those of ordinary skill in the art may be useful in the practice of this invention.

The angiogenic substance can be administered to the patient in a variety of ways. Examples of methods of administering the angiogenic substance 15 include one or more of the following steps; directly injecting the angiogenic substance into the atria, the ventricles, the veins, the arteries, and/or the formed channels; applying a slow-release formulation of the angiogenic substance into the formed channels; administering a slow-release formulation of the angiogenic substance orally, and/or via a skin patch; applying a material, such as a 20 biologically compatible or incompatible, resorbable or non-resorbable material, contacted with the angiogenic substance, over the surface of the heart; and

infusing the angiogenic substance into the patient via a pump connected to the atria, the ventricles, the veins, the arteries, and/or the formed channels.

Other examples of methods of administering the angiogenic substance include one or more of the following steps: implanting a catheter, such as a slow-release catheter, contacted with the angiogenic substance, into the atria, the ventricles, and/or the formed channels; loading a sleeve, such as an infusion sleeve, contacted with the angiogenic substance, over a catheter and introducing the catheter into the formed channels; applying bead carriers, such as heparin-alginate beads, contacted with the angiogenic substance, over the epicardial and/or endocardial surfaces of the heart; inserting an implant, such as a fibrin-glue implant, contacted with the angiogenic substance, between, for example, the aorta and the myocardium, and/or in other positions of the epicardial and/or endocardial surfaces; injecting retroviral and/or non-retroviral vectors enclosing a gene for the angiogenic substance into the myocardium, arterial walls and/or other areas of uptake, such as the skin, of the patient; infusing the angiogenic substance into veins and/or arteries; and inserting a stent, contacted with the angiogenic substance, into the formed channels. The stent can be biologically compatible or incompatible, resorbable or non-resorbable. Other methods of administration known to those of ordinary skill in the art may be useful in the practice of this invention.

In other aspects of the invention, methods for reducing angina pain, and/or enhancing myocardial perfusion and/or cardiac function include forming

at least one channel in the myocardium of a patient, and administering to the patient at least one angiogenic substance capable of stimulating growth of blood vessels in the patient. In alternative embodiments of the invention, the channel forming step can include forming the channel to link epicardial and endocardial surfaces of the heart. The method can also be employed in conjunction with implanting and/or removing a VAD. In other embodiments of the invention, the angiogenic substances and/or methods for administering the same discussed above can be used.

In still other aspects of the invention, methods for reducing angina pain, and/or enhancing myocardial perfusion and/or cardiac function include forming at least one channel in the myocardium of the patient, and inserting into the channel at least one stent contacted with one or a mixture of angiogenic substances capable of stimulating the growth of blood vessels in the patient. In embodiments of the invention, the stent can be biologically compatible or incompatible, and the channel forming step can include forming the channel to link epicardial and endocardial surfaces of the heart. The method can also include implanting and/or removing a VAD. The angiogenic substances and/or methods for administering the same discussed above can be used with these aspects of the invention.

In further aspects of the invention, devices for reducing angina pain, and/or enhancing the myocardial perfusion and/or cardiac function of a patient are disclosed that include a stent contacted with at least one angiogenic

substance capable of stimulating the growth of blood vessels in the patient and adapted for insertion into a channel formed in a myocardium of the heart of the patient. In embodiments of the invention, the stent can be biologically compatible or non-compatible, resorbable or non-resorbable. The devices of the invention
5 can be self-expanding; and/or can further include an element for expanding the stent from a first to a second position. The angiogenic substances discussed above can be used in these aspects of the invention.

In other aspects of the invention, devices for reducing angina in a patient and/or enhancing the myocardial perfusion and/or cardiac function of a
10 patient are disclosed that include an element for directing a selected beam of radiation for a pre-determined time period to a heart of the patient, and an element for administering to the patient at least one angiogenic substance capable of stimulating growth of blood vessels in the patient. The angiogenic substances discussed above can be used in these aspects of the invention.

15 In still other aspects of the invention, devices for reducing angina in a patient and/or enhancing the myocardial perfusion and/or cardiac function of a patient are disclosed that include an element for forming at least one channel in a myocardium in a heart of the patient, and an element for administering to the patient at least one angiogenic substance capable of stimulating growth of blood
20 vessels in the patient. The angiogenic substances discussed above can be used in these aspects of the invention.

In sum, the present invention benefits from the recognition that TMLR procedures and/or procedures for forming channels in the myocardium can be performed in conjunction with the administration of angiogenic substances capable of stimulating the growth of blood vessels in a patient. The methods and
5 devices of the present invention have several advantages over the prior art. In comparison with current TMLR procedures and/or procedures for forming channels in the myocardium, the present invention can improve in patients the level of angina pain reduction, and/or enhance myocardial perfusion and/or cardiac function. Accordingly, the present invention can improve the treatment
10 of disorders associated with reduced myocardial perfusion such as angina and/or improve cardiac functions in patients experiencing different levels of heart failure. In addition, the present invention can expand the pool of patients who can be eligible for TMLR procedures and/or procedures involving the formation of channels in the myocardium.

15 It will be understood that the above description pertains to only several embodiments of the present invention. That is, the description is provided by way of illustration and not by way of limitation. The invention is further characterized according to the following claims.

What Is Claimed Is:

1. A method for reducing angina in a patient comprising:

5 directing a selected beam of radiation for a predetermined time period to a heart of the patient; and

administering to the patient at least one angiogenic substance capable of stimulating growth of blood vessels in the patient.

10 2. A method for enhancing myocardial perfusion in a patient comprising:

directing a selected beam of radiation for a predetermined time period to a heart of the patient; and

15 administering to the patient at least one angiogenic substance capable of stimulating growth of blood vessels in the patient.

3. A method for enhancing cardiac function in a patient comprising:

directing a selected beam of radiation for a predetermined time period to a heart of the patient; and

20 administering to the patient at least one angiogenic substance capable of stimulating growth of blood vessels in the patient.

4. A method for reducing angina in a patient comprising:

forming at least one channel in a myocardium of the patient; and
administering to the patient at least one angiogenic substance
5 capable of stimulating growth of blood vessels in the patient.

5. A method for reducing angina in a patient comprising:

forming at least one channel in a myocardium of the patient; and
10 inserting at least one stent contacted with at least one angiogenic
substance capable of stimulating growth of blood vessels in the patient
into the channel.

6. An apparatus for reducing angina in a patient comprising:

15 a stent contacted with at least one angiogenic substance capable of
stimulating growth of blood vessels in the patient and adapted for
insertion into a channel formed in the myocardium of the patient.

7. An apparatus for reducing angina in a patient comprising:

means for directing a selected beam of radiation for a pre-determined time period to a heart of the patient; and

5 means for administering to the patient at least one angiogenic substance capable of stimulating growth of blood vessels in the patient.

8. An apparatus for reducing angina in a patient comprising:

10 means for forming at least one channel in a myocardium of the patient; and

means for administering to the patient at least one angiogenic substance capable of stimulating growth of blood vessels in the patient.

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US97/10024

A. CLASSIFICATION OF SUBJECT MATTER

IPC(6) :A61B 19/00

US CL :128/898; 623/1

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 128/898; 427/2.3, 2.25; 600/36; 604/890.1; 606/108; 623/1, 2, 12, 66, 900, 901

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

APS, DIALOG

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US 5,464,650 A (BERG et al.) 07 November 1995, entire document.	1-8
Y,P	US 5,527,337 A (STACK et al.) 18 June 1996, entire document.	1-8
Y	US 5,287,861 A (WILK) 22 February 1994, entire document.	1-8
A	US 5,429,144 A (WILK) 04 July 1995, entire document.	1-8
Y	LEE et al. Effects of laser irradiation delivered by flexible fiberoptic system on the left ventricular internal myocardium. American Heart Journal, September 1983. Volume 106 Number 3, pages 587-590.	1-8



Further documents are listed in the continuation of Box C.



See patent family annex.

* Special categories of cited documents:	*T	later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
A document defining the general state of the art which is not considered to be of particular relevance	*X*	document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
E earlier document published on or after the international filing date	*Y*	document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
L document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	*A*	document member of the same patent family
O document referring to an oral disclosure, use, exhibition or other means		
P document published prior to the international filing date but later than the priority date claimed		

Date of the actual completion of the international search

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25 SEP 1997

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INTERNATIONAL SEARCH REPORT

International application No.

PCT/US97/10024

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	ISNER et al. The Current Status of Lasers in Treatment of Cardiovascular Disease. IEEE Journal of Quantum Electronics. December 1984. Vol. QE-20. No. 12, pages 1406-1420.	1-8